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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,350	03/12/2004	Valery Krasnoperov	VASG-P01-002	2293
28120 7590 01/08/2007 FISH & NEAVE IP GROUP ROPES & GRAY LLP ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624			EXAMINER AEDER, SEAN E	
			ART UNIT	PAPER NUMBER
			1642	
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			01/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/800,350

Applicant(s)

KRASNOPEROV ET AL.

Examiner

Sean E. Aeder, Ph.D.

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**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 12 December 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: none.  
Claim(s) objected to: none.  
Claim(s) rejected: 26-29, 32-34 and 63-68.  
Claim(s) withdrawn from consideration: 35-26-29, 32-34, and 63-68.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see the attachment.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_  
13. ☐ Other: \_\_\_\_\_.

Continuation of 5. Applicant's reply has overcome the following rejection(s): the rejection of claims 63-64 under 35 U.S.C. 101 and the 35 U.S.C. 112, first paragraph, new matter rejection of claims 26-34 and 63-68.

***Advisory Action***

The Amendments and Remarks filed 12/12/06 in response to the Office Action of 8/16/06 are acknowledged and have been entered.

Claims 26-29, 32-56, and 63-68 are pending.

Claims 35-56 have been withdrawn.

Claims 26, 34, 63, and 64 have been amended by Applicant.

Claims 26-29, 32-34, and 63-68 are currently under examination.

The text of those sections of Title 35 U.S.C. code not included in this Office Action can be found in a prior Office Action.

***Rejections Withdrawn***

The rejection of claims 63 and 64 under 35 U.S.C. 101 is withdrawn.

The rejection of claims 26-29, 32-34, and 63-68 under 35 U.S.C. 112 first paragraph, for failing to comply with the written description requirement, is withdrawn.

***Rejections Maintained***

***Provision Nonstatutory Obviousness-Type Double Patenting***

Claims 26-29 and 32-34 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting, and newly added claims 63-68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-23 of copending Application No. 10/949,720.

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Although the conflicting claims are not identical, they are not patentably distinct from each other because the antibodies of claims 1-23 of 10/949,720 anticipate the claimed cells and the genus of antibodies which bind to the extracellular domain of an EphB4 protein and inhibit activities of Ephb4 recited in the pending claims.

In the remarks filed 12/12/06, Applicant requests that the Examiner hold this rejection in abeyance until allowable subject matter is found: at which point, Applicants will submit a terminal disclaimer if deemed necessary.

**35 USC § 103(a)**

The rejection of claims 26-29, 32-34, and 63-68 as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Stephenson et al (BMC Molecular Biology, 12/21/01, 2(15): 1-9) in view of Queen et al (US Patent 5,693,762; 12/2/97) for the reasons stated in the Office Action of 8/16/06 and for the reasons set-forth below.

In response to the Office Action of 8/16/06, Applicant amended claims 26, 34, 63, and 64. Further, Applicant argues that the cited references fail to provide any motivation leading the skilled artist to combine the teaching of Stephenson et al and Queen et al. Applicant further argues that Stephenson et al does not teach that inhibition of EphB4 would promote apoptosis in colon cancer cells. Applicant states that Stephenson et al does not suggest that one could use inhibitors of either Eph receptors or Ephrin as anti-cancer therapeutics. Applicant further states that Stephenson et al teaches that the role of EphB4 and other Eph receptor family members in cancer has not yet been defined. Applicant further states that the cited references fail to provide a

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reasonable expectation of success that antibodies to EphB4 would be effective in promoting apoptosis.

The amendments to the claims and the arguments found in the remarks filed 12/12/06 have been carefully considered, but are not deemed persuasive. In regards to the argument that the cited references fail to provide any motivation leading the skilled artist to combine the teaching of Stephenson et al and Queen et al, the Office Action of 8/16/06 states: **"Stephenson et al teaches that EphB4 protein is expressed on colon cancer tissues and either not at all, or in only low levels, in normal tissue (see Figure 4, in particular). Stephenson further teaches that therapies targeting EphB4 protein could be used in anticancer treatments (see page 2 left column, in particular). Due to the expression pattern of EphB2 protein, one of skill in the art would recognize that antibodies against EphB2 protein would also be used in methods of diagnosing colon cancer."** Further, the Office Action of 8/16/06 clearly states: "...one would have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled bispecific antibodies because bispecific antibodies would function as diagnostic and therapeutic agents that recruit effector molecules (toxins, drugs, prodrugs, cytokines, radionucleotides) or effector cells (cytotoxic T lymphocytes, NK cells, macrophages, granulocytes) to the colon cancer cells expressing EphB4. Further, one have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled single chain antibodies because said antibodies would be more successful at targeting diagnostics and therapeutics to EphB4 expressing colon cancer cells than the entire immunoglobulin molecule taught by

Stephenson et al. Further, one would have been motivated to create said radioisotope, fluorescent, enzyme, and enzyme co-factor labeled chimeric antibodies since chimeric antibodies have shown some therapeutic success. Further, one would have been motivated to isolate said human antibodies and to create radioisotope, fluorescent, enzyme, and enzyme co-factor labeled humanized antibodies because, as compared to non-recombinant mouse monoclonal antibodies and non-recombinant rabbit polyclonal antibodies, human and humanized antibodies would be more effective diagnostically and therapeutically effective because they are expected to (i) interact better with the human immune system (i.e. CDC and ADCC), (ii) reduce the HAMA response and (iii) the humanized antibodies will presumably have a longer half-life more similar to naturally occurring human antibodies, allowing smaller and less fragment doses to be given. Further, cells and transgenic animals expressing single chain, chimeric, and humanized antibodies specific for the extracellular domain of EphB4 would be created while creating the antibodies taught by the combined teachings of Stephenson et al and Queen et al.” Further, one of skill in the art would recognize that the bispecific, single-chain, chimeric, human, and humanized antibodies taught by the combined teachings of Stephenson et al and Queen et al would be monoclonal.

In regard to the arguments that Stephenson et al does not teach that inhibition of EphB4 would promote apoptosis in colon cancer cells, arguments that the prior art does not suggest that one could use inhibitors of either Eph receptors or Ephrin as anti-cancer therapeutics, arguments that the role of EphB4 and other Eph receptor family members in cancer has not yet been defined, and arguments that the cited references

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fail to provide a reasonable expectation of success that antibodies to EphB4 would be effective in promoting apoptosis, it is first noted that the pending claims are drawn to a product and not to a therapeutic method. Further, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation of the prior art's function, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F. 3d 1324, 1374, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus, the claiming of the unknown property of inducing apoptosis, which is inherently present in the combined teachings of the prior art, does not make the pending claims patentable. In the absence of evidence to the contrary, the combined teaching of Stephenson et al and Queen would predictably produce the antibodies recited in the pending claims.

The rejection of claims 26-29, 32-34, and 63-68 as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Inada et al (Blood, 1997, 89(8):2757-2765), in view of Stephenson et al (BMC Molecular Biology, 12/21/01, 2(15):1-9), in further view of Queen et al (US Patent 5,693,762; 12/2/97) for the reasons stated in the Office Action of 8/16/06 and for the reasons set-forth below.

In response to the Office Action of 8/16/06, Applicant amended claims 26, 34, 63, and 64. Applicant further states that Inada et al does not suggest or teach any therapeutic use or potential of the EphB4 antibody. Applicant further states that absent any teaching in Inada et al that the EphB4 antibody may have any therapeutic value, one of ordinary skill would not have been motivated to modify Inada's antibodies to



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make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4. Applicant further states that Examiner has failed to show that a skilled artisan would have predicted with a reasonable expectation of success that EphB4 antibody is capable of promoting apoptosis in a tumor cell.

The Response to the Office Action of 8/16/06 has been carefully considered, but not deemed persuasive. In regards to the argument that Inada et al does not suggest or teach any therapeutic use or potential of the EphB4 antibody, the pending claims are drawn to a product and not a method. In regards to the argument that one of ordinary skill would not have been motivated to modify Inada's antibodies to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4, one would have been motivated to modify the antibodies using methods taught by Queen et al (to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4; see previous 103 rejection) since Stephenson et al teaches that antibodies against EphB2 protein would be used in methods of diagnosing colon cancer and one of skill in the art would recognize that, from the teachings of Stephenson et al, antibodies against EphB2 protein would be useful in methods of diagnosing colon cancer.

In regards to the argument that Examiner has failed to show that a skilled artisan would have predicted with a reasonable expectation of success that EphB4 antibody is capable of promoting apoptosis in a tumor cell, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation of the prior art's function, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F. 3d 1324, 1374, 51 USPQ2d 1943,

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1947 (Fed. Cir. 1999). Thus, the claiming of the unknown property of inducing apoptosis, which is inherently present in the combined teachings of the prior art, does not make the pending claims patentable. In the absence of evidence to the contrary, the combined teaching of Indada, Stephenson et al, and Queen would predictably produce the antibodies recited in the pending claims.

### ***Summary***

No claim is allowed. Prosecution is closed.

### ***Conclusion***


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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